AKZO NOBEL

August 12, 2002

Dr. Scott A. Masten
Office of Chemical Nomination and Selection
NIEHS/NTP
P.O. Box 12233
MD A3-07
Research Triangle Park, NC 27709

Dear Dr. Masten:

Akzo Nobel Chemicals Inc., as the U.S. representative of Axcentive BV, is providing comments in response to the nomination of chloramine T and its decomposition product, p-toluenesulfonamide for inclusion in the National Toxicology Program (NTP) testing program. NTP announced the nomination of these chemical substances in the *Federal Register* dated June 12, 2002 (Volume 67, No. 133, pages, 40329-40333).

The NTP Supporting Document for the nomination of both chemical substances states that "Chloramine-T was nominated by a small commercial organization for toxicology studies based on its current status as an Investigational New Animal Drug (INAD) for controlling proliferative gill disease and bacterial gill disease in aquaculture and the need for additional toxicology studies to support its safe use".

*There is no appreciable human exposure to chloramine T or p-TSA in the United State*s *in aquaculture*. There is no current human exposure to chloramine T in aquaculture because the Axcentive INAD has not yet been approved, and even when the INAD is approved, chloramine T residues will not be found in edible fish tissues (see USGS marker residue studies cited in the NTP supporting document). Further, p-TSA residues decline rapidly in fish tissues and are not even analytically detectable in fish that attain the size fit for human consumption (see USGS marker residue studies cited in the NTP supporting document).

Historically chloramine T has also been used as a disinfectant, but this use requires specific approval from the U.S. EPA under FIFRA or FDA under the FFDCA. However, for example, there are currently no FIFRA-approved uses of chloramine T as a disinfectant and therefore there is no human exposure in the U.S. in this application. The majority of the remaining uses cited in the NTP background document are either: (1) only relevant in Europe, but not in the United States, or (2) no longer used in the United States.

These two chemical substances are under active review by the U.S. FDA within its INAD program and the responsible manufacturer, Axcentive, is actively evaluating these

chemical substances for human health effects. The U.S. FDA is the federal agency authorized by the U.S. Congress under the Federal Food, Drug and Cosmetic Act (FFDCA) to ensure the safety of animal (e. g., aquaculture) drugs before these drugs are allowed on the U.S. market. Chloramine T will not be allowed in the channels of U.S. commerce for aquaculture use until FDA has concluded that the drug is safe based on the Agency's review of adequate toxicology studies.

FDA has concluded that all required genotoxicity data on chloramine T and p-TSA have now been completed. As the Manager of Toxicology & Regulatory Affairs for Akzo Nobel Chemicals Inc. representing Axcentive, the current submitter of an INAD for chloramine T, I have been very diligently working with the U.S. FDA Center for Veterinary Medicine (CVM) to identify FDA mammalian safety issues and to generate new genotoxicity test data to satisfy those issues. We have been actively engaged in providing *in vivo* and *in vitro* genotoxicity safety studies to FDA and in a letter dated July 19, 2002 FDA has now stated that Axcentive has completed all needed genotoxicity studies on chloramine T and p-TSA.

FDA has concluded that both chemical substances are not mutagenic. The genotoxicity study reports that were reviewed and accepted by FDA on chloramine T and p-TSA have shown no genotoxic activity. For example, most recently FDA has specifically concluded in its July 19, 2002 letter that p-TSA is not mutagenic.

Therefore, there is no further need to test chloramine T and p-TSA as described in the June 12, 2002 Federal Register notice because the first tier tests (genotoxicity) have already been completed and accepted by FDA as showing no genotoxicity. The June 12, 2002 Federal Register indicated that sub chronic and/or carcinogenicity tests may be considered when the results of genotoxicity tests are available. These genotoxicity test results are now available and they are uniformly negative. FDA is not requiring that any additional genotoxicity tests be conducted on either chloramine T or p-TSA.

However, because these test reports are considered proprietary to Axcentive under its INAD, I suggest that you directly contact Dr. L.T. Mulligan, CVM, for specific confirmation of the FDA conclusions with respect to these reports as follows:

Dr. L.T. Mulligan
Supervisory Team Leader, Toxicology Team
Division of Human Food Safety
CVM, Office of New Animal Drug Evaluation
U.S. Food and Drug Administration
(301) 827-6984

. If you are unable to reach Dr. Mulligan or require specific details regarding the Axcentive genotoxicity study reports, please contact me directly. I am suggesting this approach in order to help maintain the proprietary nature of the test reports. If this approach is not workable from the standpoint of NTP please contact me directly and we can agree to a suitable alternative.

Based on the information presented above, we conclude that chloramine T and it decomposition product p-TSA should be dropped from further consideration in the NTP

testing program based on a review of the NTP selection criteria (NTP, 2000). For example, these substances do not have a high potential for adversely impacting public health because there is minimal human exposure in the U.S. in aquaculture and because these two substances have already been judged to be not genotoxic by FDA. Also, there is no technical reason to indicate that the testing of these two substances will enhance the predictive ability of future NTP studies because it has already been concluded that chloramine T would not be carcinogenic in the NTP bioassay program (Tennant, 1990).

In addition, these two substances should be deleted from further testing consideration based on a review of the NTP nomination principles (NTP, 2002). For example, the two substances are closely associated with a single commercial organization with respect to aquaculture: Axcentive. These substances have already been adequately evaluated and there is no need for further federal involvement and the aquaculture use of chloramine T has been reviewed according to current FDA testing requirements. Nor is Federal involvement required in this case to assist in the development of potential substitutes for existing products.

The limited resources of the NTP should be used to address scientific issues of higher interest and current need to the U.S. population, but not those issues that can and are already being adequately addressed by other federal programs. In this case, there is basically no human exposure to chloramine T or p-TSA in the aquaculture area because FDA has not yet approved its animal drug use, nor to our knowledge does chloramine T have any other regulatory approval in the U.S. In addition, FDA has already concluded that sufficient genotoxicity data are available on chloramine T and p-TSA, and further that these substances are not genotoxic. Therefore, based on a lack of any significant human exposure and based on the completeness of the current genotoxicity database we are requesting that NTP delete chloramine T and p-TSA from the June 12, 2002 nomination list.

We will be very interested in attending the open public session of the NTP Board of Scientific Counselors that will review these two substances. Please provide me with the data and location of this public meeting.

Respectfully submitted,

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REFERENCES CITED

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